The Epidemiology of Severe Acute Respiratory Syndrome in the 2003 Hong Kong Epidemic: An Analysis of All 1755 Patients

Gabriel M. Leung, MD, MPH; Anthony J. Hedley, MD, FRCP; Lai-Ming Ho, PhD; Patsy Chau, MStat; Irene O.L. Wong, MPhil, MMedSc; Thuan Q. Thach, PhD; Azra C. Ghani, PhD; Christl A. Donnelly, ScD; Christophe Fraser, PhD; Steven Riley, DPhil; Neil M. Ferguson, DPhil; Roy M. Anderson, PhD; Thomas Tsang, MBBS, FHKAM; Pak-Yin Leung, MBBS, FFPH; Vivian Wong, MBBS, FHKAM; Jane C.K. Chan, MD, FHKAM; Eva Tsui, MStat; Su-Vui Lo, MBChB, FFPH; and Tai-Hing Lam, MD, FFPH

Background: **As yet, no one has written a comprehensive epidemiologic account of a severe acute respiratory syndrome (SARS) outbreak from an affected country.**

Objective: **To provide a comprehensive epidemiologic account of a SARS outbreak from an affected territory.**

Design: **Epidemiologic analysis.**

Setting: **The 2003 Hong Kong SARS outbreak.**

Participants: **All 1755 cases and 302 deaths.**

Measurements: **Sociodemographic characteristics; infection clusters by time, occupation, setting, and workplace; and geospatial relationships were determined. The mean and variance in the time from infection to onset (incubation period) were estimated in a small group of patients with known exposure. The mean and variance in time from onset to admission, from admission to discharge, or from admission to death were calculated. Logistic regression was used to identify important predictors of case fatality.**

Results: **49.3% of patients were infected in clinics, hospitals, or elderly or nursing homes, and the Amoy Gardens cluster accounted for 18.8% of cases. The ratio of women to men among infected individuals was 5:4. Health care workers accounted for 23.1% of all reported cases. The estimated mean incubation period was 4.6 days (95% CI, 3.8 to 5.8 days). Mean time from symptom onset to hospitalization varied between 2 and 8 days, decreasing over the course of the epidemic. Mean time from onset to death was 23.7 days (CI, 22.0 to 25.3 days), and mean time from onset to discharge was 26.5 days (CI, 25.8 to 27.2 days). Increasing age, male sex, atypical presenting symptoms, presence of comorbid conditions, and high lactate dehydrogenase level on admission were associated with a greater risk for death.**

Limitations: **Estimates of the incubation period relied on statistical assumptions because few patients had known exposure times. Temporal changes in case management as the epidemic progressed, unavailable treatment information, and several potentially important factors that could not be thoroughly analyzed because of the limited sample size complicate interpretation of factors related to case fatality.**

Conclusions: **This analysis of the complete data on the 2003 SARS epidemic in Hong Kong has revealed key epidemiologic features of the epidemic as it evolved.**

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For author affiliations, see end of text.

Severe acute respiratory syndrome (SARS) was the first newly emergent communicable disease epidemic of the 21st century. During the first epidemic of this new pathogen, 29 countries were affected. The first human case was identified in Guangdong, China, on 16 November 2002 (1), and the last known case with a symptom onset date of 5 July 2003 was identified in Taiwan. The epidemic reportedly infected 8098 individuals, 774 of whom died (2). Hong Kong bore a large proportion of this morbidity and mortality burden: 1755 cases and 302 deaths occurred from 15 February to 31 May 2003. Hong Kong also provided the link between the cases in China and those in other parts of the world. The resurgence of SARS is distinctly possible given its uncertain origins and the likely existence of an animal reservoir, the palm civet cat (3). Since the end of the first major epidemic in July 2003, 4 new cases were reported from Guangdong province in China in late 2003 and early 2004.

An account of the epidemiology of SARS in Hong Kong was undertaken during the outbreak (4) to inform public health policymaking. The data set has since been updated by using information of all 1755 reported cases, allowing for the relaxation of parametric assumptions, necessary in the mid-epidemic analysis, in the analysis of the times from symptoms to admission, admission to death, and admission to discharge. Furthermore, complete case data of the closed cohort allow analysis of predictors of SARS-related death by using logistic regression. We present an epidemiologic analysis of the SARS outbreak in Hong Kong on the basis of all reported cases and deaths classified according to prevailing World Health Organization (WHO) guidelines. In addition, laboratory verification by reverse transcriptase polymerase chain reaction (RT-PCR) test or SARS coronavirus antibody serologic test was obtained for 83.6% of cases. On the basis of the complete data set, we present the following analyses: a detailed description of the temporal and spatial evolution of the epidemic; the estimates of key epidemiologic distributions and their stability over the course of the epidemic; and the characteristics of those who contracted the disease, including factors associated with the likelihood of death from SARS coronavirus infection.

Methods

Sources of Data

We analyzed an integrated database (SARSID), derived from the Hong Kong Hospital Authority eSARS system and the Hong Kong Department of Health's master list, which contained details on all patients reported to have SARS who were hospitalized in Hong Kong throughout the epidemic. The eSARs system is a secure, Web-based data repository that contains mostly real-time clinical data entered on the SARS patient wards. Trained nurses retrospectively collected and confirmed some data fields by a detailed chart review according to a standardized protocol. The Hong Kong Department of Health's master list mostly consisted of information from the questionnaires of case and case contact data. We administered the questionnaires (containing case and case contact information), mostly through telephone interviews, to all patients with SARS confirmed by the Hong Kong Department of Health; in most cases, the questionnaire was administered within 3 days (up to a maximum of 1 week) of initial presentation with SARS. For patients who could not be contacted or who were too ill to be interviewed, we obtained proxy reporting from an immediate family member who was most familiar with the medical and contact history of the patient before infection. Four regional field offices initially administered these questionnaires, and a central interviewing team of nurses later recorded symptoms at presentation to the hospital and identified contacts and events of probable significance to transmission. We collected data on case and contact information for all 1755 patients with SARS, although we did not complete all data elements for all cases. The Appendix (available at www.annals.org) provides detailed clinical case definitions for SARS throughout the 2003 epidemic.

We based laboratory confirmation of SARS on laboratory techniques that were consistent with the WHO case definition for laboratory confirmed SARS (5): 1) RT-PCR for SARS coronavirus and 2) serologic testing for IgG antibodies against SARS coronavirus. A patient was considered to have laboratory-confirmed SARS if there was a positive RT-PCR result from 2 or more clinical specimens, either from different sites or tested in different laboratories, obtained from patients before or after death or if there was seroconversion by enzyme-linked immunosorbent assay (ELISA), indirect fluorescent antibody test, or neutralization assay. Although these tests were mostly available during the outbreak, not all patients were tested for any or all of them for various reasons, including nonuniform testing protocol (especially in the earlier part of the outbreak), lack of samples due to early case fatality without autopsy examination, and inadequate and missing specimens. Test variables, such as sensitivity and specificity, were unknown because there were no "gold standard" laboratory or clinicopathologic definitions for the diagnosis of SARS, a new and emerging disease, for comparing diagnostic test performance. The IgG antibodies against SARS coronavirus found on serologic testing seemed to be the best method for confirming SARS in largely seronegative populations (6), where the reported seropositivity rate reached 93% to 99% in Hong Kong (7, 8) and 96.2% in Toronto (9). We collected paired serologic specimens at least 21 to 28 days apart, although anecdotal reports of longitudinal follow-up of patients with SARS in Hong Kong estimate that seroconversion can occur as long as 6 months after acute illness. Tang and colleagues (9) found that the sensitivity of 1 first-generation RT-PCR was 54.1% in their Toronto SARS case series, assuming that all clinically classified patients truly had SARS. These findings were broadly similar to those reported by Peiris and colleagues (8) for the outbreak at Amoy Gardens housing estate in Hong Kong during late March and early April. In both the Hong Kong and Toronto epidemics (8, 9), the peak rate of RT-PCR positivity occurred 9 to 11 days after first symptoms presented, and gastrointestinal specimens gave higher yields than respiratory samples. Poon and colleagues (10) later produced a second-generation RT-PCR assay capable of detecting SARS coronavirus in up to 88% of respiratory tract samples obtained within the first 3 days after illness onset in confirmed SARS cases in the Hong Kong outbreak. This test kit was adopted in the latter part of the Hong Kong epidemic. All SARS coronavirus specimen testing in Hong Kong was performed in 3 designated laboratories (Chinese University of Hong Kong, University of Hong Kong, and Hong Kong Department of Health) where rigorous quality control procedures were established. The World Health Oranization and members of the WHO SARS Reference and Verification Laboratory Network certified all 3 facilities as reference laboratories.

Context

Few comprehensive studies describe the 2003 outbreak of severe acute respiratory syndrome (SARS).

Contribution

This epidemiologic analysis of 1755 cases from Hong Kong found that most cases clustered in hospitals and residential buildings. Close human contact and spread by a sewage system probably explain the clustering. The outbreak lasted about 3 months. The estimated mean incubation period was 4.6 days, and the case-fatality ratio was 17%. Factors associated with increased risk for death included older age and male sex.

Implications

The observed patterns suggested that SARS had low transmissibility, except in settings of intimate contact or clinically significant environmental contamination.

–The Editors

Statistical Analysis

We constructed the epidemic time series on the basis of all 1755 local cases by date of symptom onset and infection cluster. We classified infection clusters by probable transmission setting (institutional vs. community spread), location (for example, housing estates), occupation (for example, health care workers in public and private sectors), and workplace (for example, hospitals and other buildings). We compared the age and sex distributions of SARS cases with general population estimates derived from the 2001 population census conducted by the Hong Kong Government Census and Statistics Department.

To illustrate the geospatial pattern of infection and disease spread, we used a geographic information system (ArcGIS, Environmental Systems Research Institute, Redlands, California) to construct a map of infection clusters in different districts of Hong Kong.

We plotted empirical distributions for times from onset to admission, onset to death, and onset to discharge after recovery (from acute care since many patients were transferred to convalescent facilities), and we calculated the mean and variance of these distributions (Appendix, available at www.annals.org). Infection events cannot be observed, but data on patients with short and well-defined periods of 1 exposure to known SARS cases can be used to estimate the distribution of the time from infection to onset of symptoms (the incubation period) by using methods for interval-censored data (4, 11). The database contained 81 patients who had 1 exposure to a confirmed SARS case over a limited time scale ($<$15 days) with recorded start and end dates, who did not travel, and who were not hospitalized before the onset of symptoms. We estimated the distribution by using maximum likelihood methods, assuming a γ distribution.

We used logistic regression to identify factors significantly associated with case fatality due to SARS. The following variables were tested in the model: age; sex; occupation (health care worker vs. others); symptoms on presentation (typical [patients with SARS whose symptom score as determined by the prediction rule was above the threshold designated as high risk for SARS] vs. atypical [patients with SARS whose score was below the threshold designated as low risk for SARS], as determined according to a clinical prediction model reported separately [12]); infection cluster; calendar period of infection as defined by the symptom onset date; time from onset to admission; presence of preexisting comorbid conditions (including asthma, chronic obstructive pulmonary disease, cardiovascular disease, cerebrovascular disease, cancer, diabetes mellitus, chronic renal disease, and chronic liver disease); lactate dehydrogenase level as a ratio to the upper limit of normal as an indicator of disease severity on admission; and time (days) between the onset of symptoms and initiation of ribavirin therapy. We entered factors into the model on the basis of hypotheses about possible candidate predictors of mortality in the literature (4, 13–15) at the time of analysis. The categorization of variables, including the assignment of the reference categories, was specified a priori. We included all patients in the logistic regression models, and we used multiple imputation methods to handle missing data items. We imputed the missing data by expectation with importance resampling algorithm (16) by using AMELIA software (Aptech Systems, Inc., Maple Valley, Washington) (17). We generated 10 imputations and analyzed them separately, and we combined the results to estimate the within-imputation and between-imputation variability (18). For sensitivity analysis, we omitted the lactate dehydrogenase level and atypical versus typical symptom variables (the 2 factors with the most missing items) from the regression equation to test the robustness of the baseline model findings.

We plotted the probability of survival or mortality curves stratified by age to illustrate the dependence of time to death for those who died with these demographic variables.

We repeated these analyses on the 1467 patients with laboratory confirmation of SARS. We used Stata, version 8.0 (Stata Corp, College Station, Texas), for all statistical analyses.

Role of the Funding Sources

The funding sources had no role in the design, conduct, and reporting of the study or in the decision to submit the manuscript for publication.

RESULTS

Laboratory Confirmation of SARS Status

Of the 1755 patients, 1467 patients (83.6%) met the prespecified criteria for laboratory confirmation of SARS: 447 seroconverted and had 2 or more positive RT-PCR results, 959 seroconverted only, and 61 had 2 or more positive RT-PCR results only. The remaining 288 patients did not meet criteria for laboratory confirmation for various reasons, such as inadequate or insufficient specimens (n = 199) or negative RT-PCR or serologic test results (n = 89).

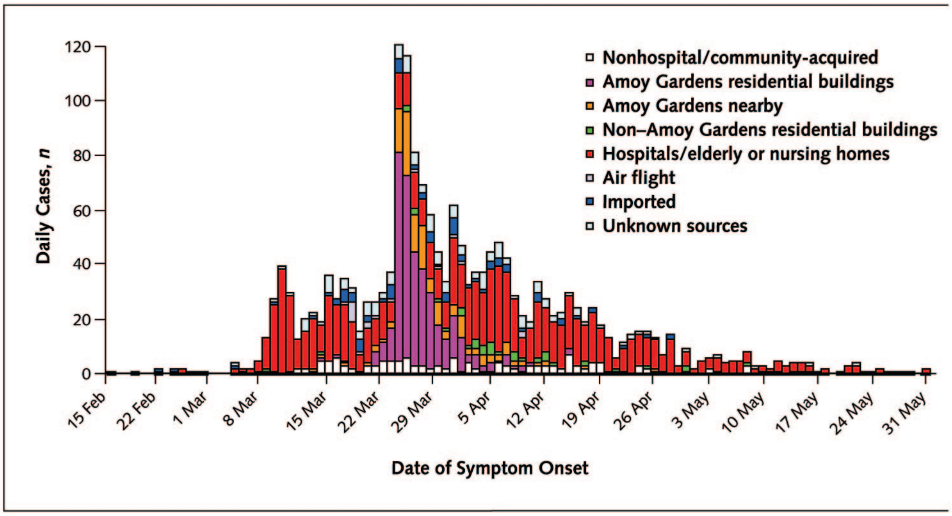
Time

The patient who initiated the largest transmission chain throughout the territory and who, in turn, seeded the global outbreak, was a medical professor from Guangdong province in mainland China who first showed symptoms on 15 February and was subsequently hospitalized on 22 February, 1 day after arriving in Hong Kong (19). The development of the epidemic featured a period of exponential growth, beginning on 10 March, after the formal announcement of the outbreak, which was further exacerbated by transmission not related to intimate personal contact, probably through the sewage system (19), in Amoy Gardens residential buildings and their immediate neighborhood. A period of comparative stability in early to mid-April occurred, with evidence of weakening beginning the week of 22 April. The last patient with SARS first experienced symptoms on 31 May and was hospitalized on 2 June (**Figure 1**).

Place

Figure 1 and **Table 1** show that half (49%) of the SARS cases were the result of infection in clinics, public

Figure 1. **Severe acute respiratory syndrome epidemic curve in Hong Kong, 2003, by infection cluster.**



and private hospitals, or elderly or nursing homes. Another important setting of disease spread was the superspreading event in Amoy Gardens that resulted in daily incidence counts of close to 100 cases per day at the height of the outbreak in late March. Spread within residential buildings accounted for 22% of all cases, mostly at the Amoy Gardens housing estate. We classified an additional 7% of total cases as "Amoy Gardens nearby." This label refers to patients with SARS who were living in the immediate neighborhood of Amoy Gardens and were believed to be linked to the main Amoy Gardens cluster but were not residents of the housing estate. About 5% of Hong Kong's cases were imported (or reimported) from overseas or from air travel. Fewer than 10% of all cases resulted from transmission in the general community (aside from the superspreading event in Amoy Gardens), including household settings. Of this community transmission, 64% (97 of 152 cases) could be attributed to intrafamilial or within-household spread, defined as transmission from 1 household or family member to another with no other known sources of infectious contact.

Figure 2 illustrates the geographic locations of SARS infection by patients' residential address. The size of the circle corresponds to the density of cases in a particular location. Cases clearly clustered in certain districts of the Kowloon peninsula (Kwun Tong, in which Amoy Gardens is located) and the New Territories (including Shatin and Tai Po districts where the Prince of Wales Hospital and Alice Ho Mui Ling Nethersole Hospital, sites of large nosocomial outbreaks, are situated, respectively), but Hong Kong Island was relatively spared. Clustering became apparent as the epidemic unfolded, with per capita incidence varying significantly between districts (4, 20).

People

Overall, the ratio of women to men among infected individuals was 5:4 (**Table 1**). When we compared the age and sex distribution of the Hong Kong general population, we found a clear excess of young adults, especially women (102 of 254 women with SARS 25 to 34 years of age were nurses), infected with SARS and a relative deficit of children and adolescents. Elderly men (>75 years of age) were also overrepresented among patients with SARS (**Figure 3**), as were elderly women (>75 years of age), although to a lesser extent. Health care workers made up 23% of all infected persons. **Table 2** shows that most infections occurred in the public sector (that is, within the mainly tax-financed Hong Kong Hospital Authority, which oversees all 44 public hospitals and provides 95% of total inpatient bed-days in Hong Kong, with minimal co-payments at the point of care and guaranteed universal access for all residents), where all patients with SARS were mainly cared for in 14 designated centers (some were initially admitted to other hospitals but later transferred). Nurses accounted for 52% of the 405 health care worker cases, and health care assistants (for example, orderlies) accounted for 28%. One in 7 (16%) health care workers were medical physicians.

Key Epidemiologic Variables

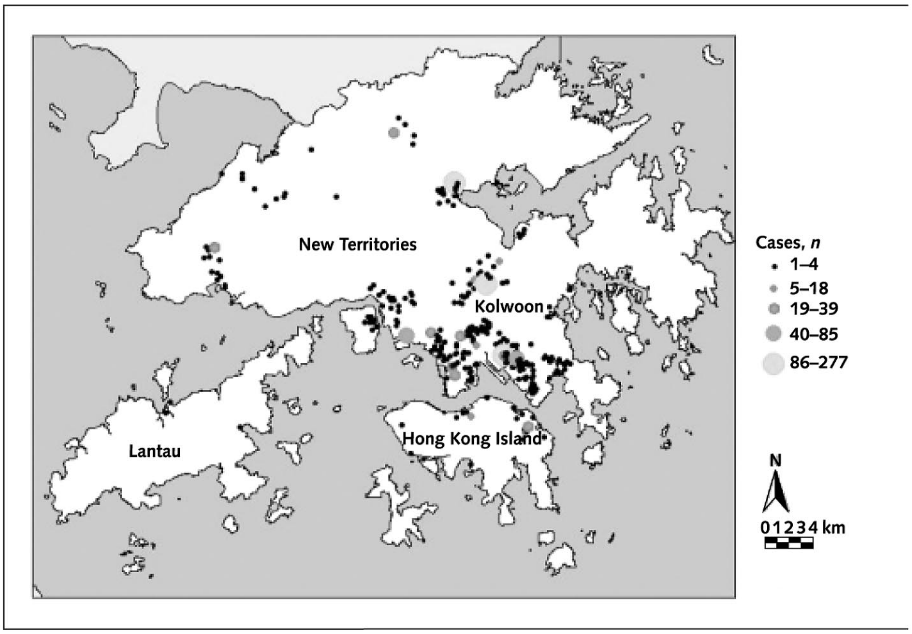
The estimated mean and variance in the incubation period distribution was 4.6 days and 15.9 days, respectively. In 95% of patients, symptoms developed within 12.5 days of infection. **Figure 4** presents the estimated distribution. This distribution is based on a limited number of observations (only 5% of the total cases) and could reflect biases in reporting, heterogeneity in routes of transmission, or varying infectious doses of the SARS coronavirus. On bivariable testing between the 81 patients for whom we estimated the incubation period and the remaining patients (data not shown), we found that none was an Amoy Gardens case and that hospital-infected cases were overrepresented. They also tended to have been infected slightly later in the epidemic. Most of the 81 patients had preexisting comorbid conditions.

Table 1. **Characteristics of Patients with Severe Acute Respiratory Syndrome, Case-Fatality Ratios, and Associated Adjusted Odds Ratios***

Characteristic	Patients, *n* (%) (*n* = 1755)	Case–Fatality Ratio, %	Adjusted Odds Ratio (95% CI)	*P* Value†
Sex				
Women	978 (55.7)	13.2	1	—
Men	777 (44.3)	22.3	1.5 (1.1–2.0)	
Age				
≤39 y	848 (48.3)	3.0	1	<0.001
40–59 y	529 (30.1)	13.4	4.2 (2.6–6.8)	
≥60 y	378 (21.5)	54.5	19.9 (11.7–33.8)	
Health care worker				
No	1350 (76.9)	21.8	1	—
Yes	405 (23.1)	2.0	0.3 (0.1–0.7)	
Atypical symptoms				
No	1446 (82.4)	15.9	1	—
Yes	36 (2.0)	52.8	1.7 (0.8–4.1)	
Unknown because of missing data	273 (15.6)	19.4	—	
Infection cluster				
Not hospital- or community-acquired	152 (8.7)	12.5	1	—
Amoy Gardens residential buildings	330 (18.8)	12.7	1.7 (0.9–3.4)	
Amoy Gardens nearby‡	128 (7.3)	14.8	1.2 (0.6–2.7)	
Non–Amoy Gardens residential buildings	47 (2.7)	21.3	2.0 (0.7–5.3)	
Hospitals or elderly or nursing homes	866 (49.3)	20.7	1.2 (0.6–2.2)	
Air flight	19 (1.1)	15.8	2.3 (0.5–10.7)	
Imported	79 (4.5)	12.7	0.7 (0.3–1.7)	
Unknown sources	134 (7.6)	14.9	1.0 (0.4–2.2)	
Symptom onset date				
15 February–14 March	198 (11.3)	13.6	1	>0.2
15–28 March	669 (38.1)	13.2	0.9 (0.5–1.6)	
29 March–11 April	501 (28.6)	16.2	0.6 (0.3–1.2)	
12–25 April	250 (14.3)	25.6	0.6 (0.3–1.2)	
26 April–31 May	137 (7.8)	30.7	0.8 (0.4–1.7)	
Onset-to-admission interval				
1 d	226 (12.9)	10.6	1	0.09§
2–3 d	554 (31.6)	13.4	1.3 (0.7–2.3)	
4–5 d	337 (19.2)	9.5	0.7 (0.3–1.4)	
6–7 d	179 (10.2)	14.0	1.0 (0.5–2.2)	
≥8 d	123 (7.0)	9.8	0.5 (0.2–1.3)	
Admitted on or before symptom onset date	336 (19.1)	40.2	2.1 (1.1–3.8)	
Preexisting comorbid conditions				
No	1396 (79.5)	10.0	1	—
Yes	359 (20.5)	45.5	1.7 (1.2–2.5)	
Lactate dehydrogenase level on admission‖				
≤0.79	380 (21.7)	9.0	1	<0.001
0.79–0.99	373 (21.3)	10.7	0.9 (0.5–1.6)	
0.99–1.37	385 (21.9)	20.6	1.7 (1.0–2.7)	
>1.37	375 (21.4)	27.3	2.3 (1.4–3.8)	
Not measured	242 (13.8)	19.2	—	
Initiation of ribavirin therapy from symptom onset				
Treatment not prescribed	97 (5.5)	22.2	1	0.11
Prescribed on day of symptom onset	32 (1.8)	18.8	1.5 (0.4–5.9)	
1–3 d	556 (31.7)	15.1	2.1 (1.0–4.3)	
4–6 d	579 (33.0)	16.4	2.1 (1.0–4.3)	
≥7 d	491 (28.0)	19.4	2.0 (1.0–4.0)	

* All variables were entered and adjusted for each other in the logistic model. Multiple imputation methods were used to handle missing data items, and results are based on the analysis of all patients.
† For linear trend.
‡ "Amoy Gardens nearby" refers to cases of severe acute respiratory syndrome that occurred in the immediate neighborhood of Amoy Gardens and were believed to be linked to the superspreading event, but the patients were not residents of the housing estate.
§ Applies to only the first 5 subcategories.
‖ Reported as a ratio to upper limit of normal.

Figure 2. **Geospatial distribution of cases of severe acute respiratory syndrome in Hong Kong (February to June 2003).**



Source: Hong Kong Department of Health.

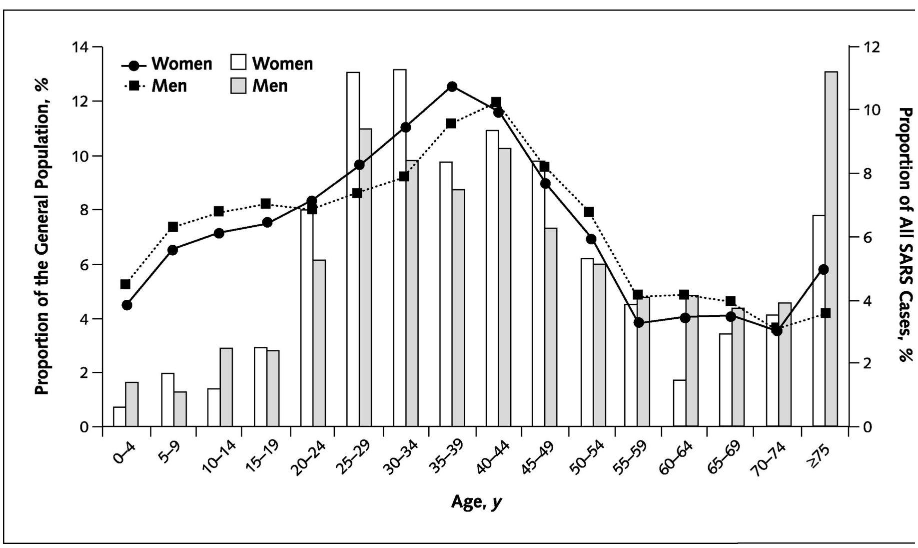
Onset and admission times are both observable events. We grouped patients by their week of clinical onset, and 11 time periods were analyzed (**Table 3**). Not enough patients with symptom onset before 15 February were available for robust analysis. **Table 3** shows mean time from onset to admission for each time period. The time from onset to admission statistically significantly decreased during the first 5 weeks but not in the last 6 weeks (**Figure 5**, *top*) (Appendix, available at www.annals.org).

The mean and variance in the time from onset to death were 23.66 days and 221.04 days^2, respectively, and the mean and variance in the time from onset to discharge from short-term care were 26.47 days and 194.90 days^2. These distributions varied substantially, with greater variance in the time from onset to death than in the time from onset to discharge (**Figure 5**, *middle* and *bottom*).

Case-Fatality Ratios and Associated Predictors

Of 1755 SARS cases, 302 patients died, yielding an overall case-fatality ratio of 17.2%. **Table 1** shows the ad-

Figure 3. **Age and sex distributions of patients with severe acute respiratory syndrome (*SARS*) compared with the Hong Kong general population.**



The solid and dotted lines refer to the proportion of the general population, and the bars refer to the proportion of all SARS cases.

Table 2. **Distribution of Infected Health Care Workers by Profession and Work Setting (*n* = 405)**

Health Care Worker	Infected Persons, *n (%)*	Case-Fatality Ratio (95% CI), %
Public hospitals		
Physicians	56 (13.8)	3.6 (0.4–12.3)
Nurses	188 (46.4)	0.5 (0.0–2.9)
Health care assistants and others	108 (26.7)	2.8 (0.6–7.9)
Medical students	16 (4.0)	0 (0.0–20.6)
Private hospitals		
Physicians	0 (0)	—
Nurses	16 (4.0)	0 (0.0–20.6)
Health care assistants and others	6 (1.5)	0 (0.0–45.9)
Private outpatient clinics		
Physicians	8 (2.0)	25.0 (3.2–65.1)
Nurses	6 (1.5)	0 (0.0–45.9)
Others	1 (0.3)	0 (0.0–97.5)
Total	405 (100.0)	2.0 (0.6–3.3)

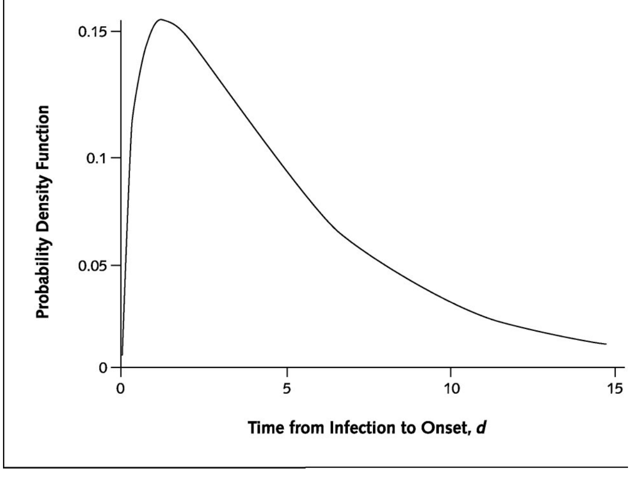
justed odds ratios and associated 95% CIs for the logistic regression model. Survival was highly associated with both age and sex (**Table 1**). Men with SARS had a 50% (95% CI, 7% to 109%) excess risk for death. Mortality increased significantly with age ($P < 0.001$). Patterns in survival curves and time to discharge curves varied by age category (**Figure 6**). A lower case-fatality ratio was associated with health care worker status (adjusted odds ratio, 0.3 [CI, 0.1 to 0.7]). The presence of preexisting comorbid conditions and greater disease severity (as proxied by high lactate dehydrogenase level on admission) were both associated with a higher risk for death. The calendar time period during which patients became ill was not statistically significantly associated with survival, and earlier admission after symptom onset and the timing of ribavirin administration were not protective. The precise infection cluster that a patient belonged to was not a significant predictor.

Analyses based on the subset of 1467 patients with laboratory confirmation of SARS generally produced results similar to those presented on the full cohort (see Appendix, **Appendix Tables 1** and **2**, and **Appendix Figures 1** and **2** for further details, available at www.annals.org). However, we note that health care worker status (adjusted odds ratio, 0.6 [CI, 0.2 to 1.3]) was no longer statistically significantly associated with survival for the subset of laboratory-confirmed SARS coronavirus cases. While we recognize that the differences between the 2 sets of data are clinically important, we believe that data from the full cohort of 1755 patients are the main results partly because 199 of 288 non–laboratory-confirmed cases did not have adequate or sufficient clinical specimens to be tested but nonetheless fulfilled clinical and epidemiologic criteria to be diagnosed as SARS before laboratory testing. This is very different from the scenario in which both RT-PCR and serologic tests were performed but the results were negative. In addition, we accounted for the influence of missing data on the stability of the logistic regression models (that is, both models of 1755 and 1467 patients) by multiple imputation and through a series of sensitivity analyses. We excluded the 2 variables with the most missing values (atypical symptoms and lactate dehydrogenase level on admission) from the regression model and performed a complete case analysis (without multiple imputation). The results were robust, achieved statistical significance, and showed similar directionality and magnitude of associations.

DISCUSSION

Our findings summarize the time course and patient location of Hong Kong's 2003 SARS outbreak and the characteristics of those infected. The time course of the epidemic was marked by an initial period of exponential growth that eventually started to decrease after 6 weeks of intensive public health control measures (22). Substantial geospatial clustering was observed, with several large clusters of SARS cases in hospital and residential settings and a high proportion of health care workers. These observations are largely consistent with those reported for the Singapore and Toronto outbreaks, where the hospital environment substantially amplified the risk for infection (14, 23, 24). The pattern of infection clusters (**Table 1**) also suggests that the transmissibility of viral infection is low, except in settings of intimate contact or where clinically significant environmental contamination has occurred. It may also suggest low infectiousness in patients for some days after the onset of clinical symptoms. In addition, the risk for acquiring infection varied significantly by age, with relatively few cases of infection and no deaths in children and adolescents. The reasons for this are unclear. One hypothesis relating to mild or asymptomatic infection in young

Figure 4. **Estimate of time from infection to onset distribution.**



Note that this graph was based on data from a small subgroup of patients fitted to a γ distribution.

Table 3. **Estimates of Key Epidemiologic Variables**

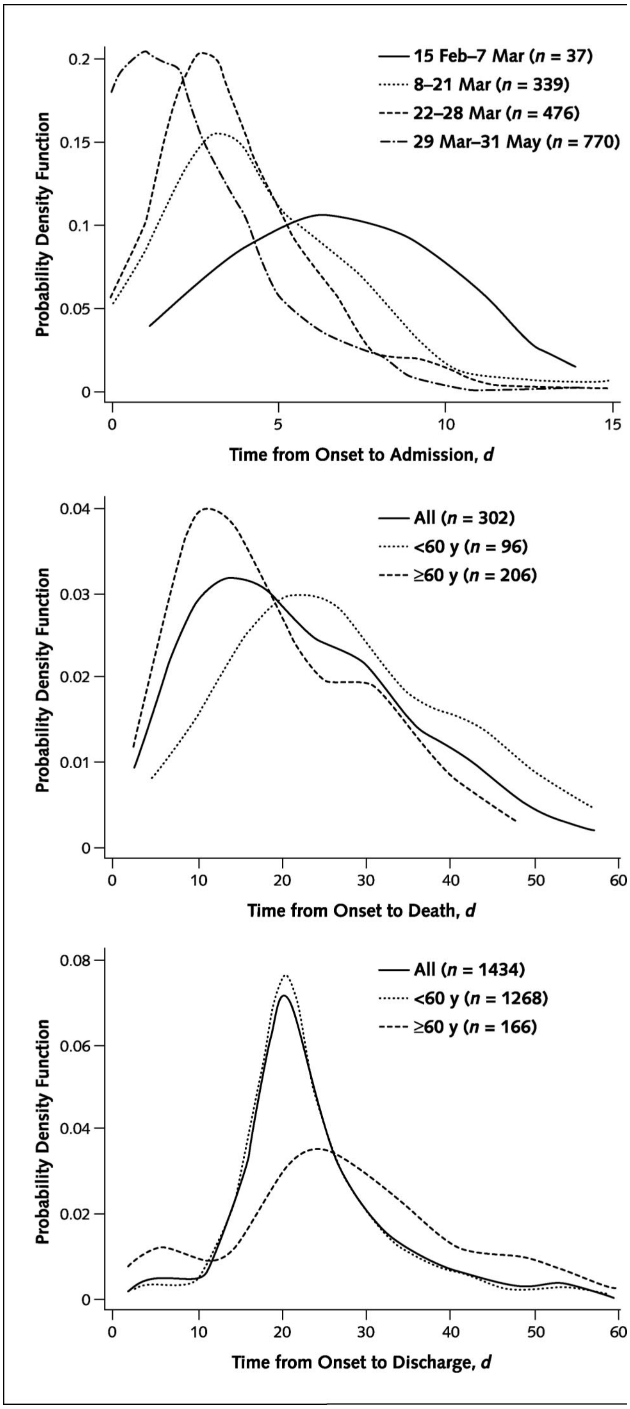
Variable	Patients, *n*	Mean Length of Time (95% CI), *d*	Median Length of Time, *d*	10th Percentile, *d*	90th Percentile, *d*
Time from infection to onset (incubation period)*	81	4.6 (3.8–5.8)	—	—	—
Time from onset to admission					
15 February–7 March	37	7.4 (5.7–9.1)	7.0	2.0	11.0
8–14 March	155	4.7 (4.3–5.1)	4.0	2.0	8.0
15–21 March	184	4.1 (3.7–4.5)	4.0	0	8.0
22–28 March	476	3.7 (3.4–3.9)	3.0	1.0	7.0
29 March–4 April	263	2.6 (2.2–2.9)	2.0	0	6.0
5–11 April	207	2.4 (2.1–2.8)	2.0	0	5.0
12–18 April	129	2.6 (2.2–3.1)	2.0	0	6.0
19–25 April	72	2.2 (1.7–2.7)	2.0	0	4.0
26 April–2 May	41	2.7 (2.0–3.4)	2.0	0	5.0
3–9 May	27	2.4 (1.6–3.3)	2.0	0	5.0
10–31 May	31	2.3 (1.4–3.1)	2.0	0	5.0
Time from onset to death					
Men					
≤29 y	2	—	—	—	—
30–39 y	11	27.0 (18.4–35.6)	26.0	16.0	35.0
40–49 y	26	31.7 (24.9–38.5)	27.5	18.0	51.0
50–59 y	18	33.6 (27.3–39.9)	35.0	14.0	48.0
60–69 y	27	23.0 (18.1–27.9)	22.0	9.0	42.0
≥70 y	89	18.8 (16.3–21.2)	16.0	6.0	36.0
Women					
≤29 y	—	—	—	—	—
30–39 y	12	29.8 (21.6–38.1)	25.5	18.0	45.0
40–49 y	13	27.7 (18.9–36.5)	23.0	11.0	46.0
50–59 y	14	38.2 (26.6–49.8)	34.5	16.0	64.0
60–69	21	28.6 (21.1–36.0)	27.0	10.0	47.0
≥70 y	69	17.7 (14.5–20.8)	13.0	6.0	38.0
Time from onset to discharge from acute care					
Men					
≤29 y	199	23.5 (22.3–24.8)	22.0	14.0	34.0
30–39 y	132	27.4 (25.0–29.9)	22.0	17.0	41.0
40–49 y	111	26.9 (24.3–29.5)	24.0	15.0	43.0
50–59 y	62	31.3 (26.4–36.2)	25.5	13.0	58.0
60–69 y	45	33.3 (26.9–39.6)	27.0	15.0	65.0
≥70 y	45	29.2 (22.9–35.5)	24.0	10.0	62.0
Women					
≤29 y	274	23.5 (22.3–24.6)	21.0	14.0	34.0
30–39 y	212	25.9 (24.1–27.7)	23.0	14.0	37.0
40–49 y	188	27.7 (25.7–29.7)	24.0	16.0	42.0
50–59 y	90	26.8 (24.0–29.6)	24.0	13.5	41.5
60–69	30	30.2 (24.5–36.0)	28.0	11.5	51.5
≥70 y	46	32.0 (25.3–38.7)	24.0	12.0	61.0

* Note that these estimates were based on data from a small subgroup of patients fitted to a γ distribution.

patients has not been borne out by detailed serologic testing of case contacts (25). Alternative hypotheses, including one that suggests that more recent infections in young patients with other coronaviruses confer some degree of protection to SARS coronavirus due to antigenic cross-reactivity, have not as yet been tested. Current prevailing theories focus on an attenuated immunopathologic response in children because of a more immature immune system (26). However, the exact mechanism that leads to SARS coronavirus–induced immunomodulation remains to be elucidated (27).

A key aspect of infection control introduced during the epidemic was a policy of quarantine, in which individuals who were possibly infected or had contact with known SARS cases were isolated for a fixed period. This period was defined by timely estimates of the time from exposure to first symptoms (that is, the incubation period distribution) (4, 28). Our analyses of the full data set suggest that the duration of quarantine may need to be reconsidered. The World Health Organization and the Centers for Disease Control and Prevention currently recommend a period of 10 days, but our results indicate that 13 days may be necessary to capture 95% of all possible cases (2, 29). We stress that our estimation procedure adopted a parametric γ distribution and thus implicitly assumed the possibility of very long incubation periods. Another caveat is that, because of methodologic constraints, this distribution was fitted to data on a very small subset of cases with a single exposure source with known start and end dates; thus, the generalizability of these findings to the whole

Figure 5. **Estimates of onset-to-admission, onset-to-death, and onset-to-discharge distributions.**

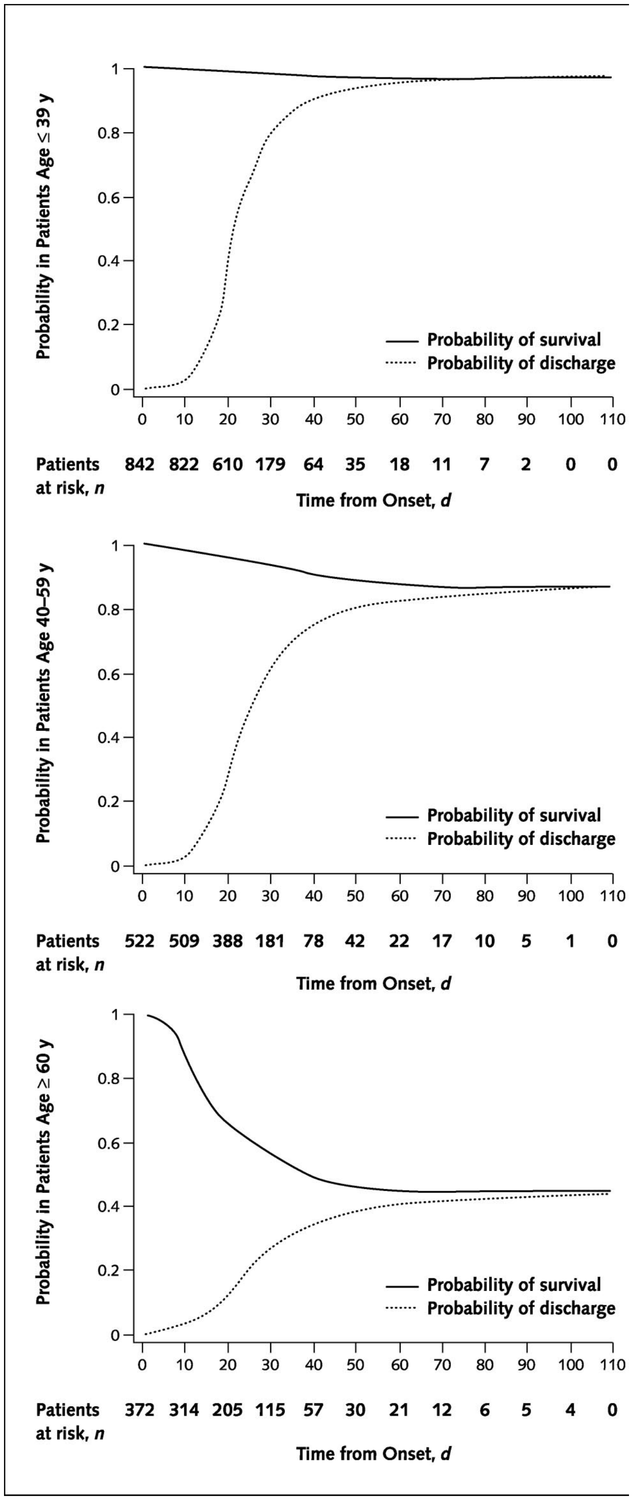


Estimates of time-dependent onset-to-admission distribution as a function of time of onset of clinical symptoms (*top*), onset-to-death distribution by patients' age (*middle*), and onset-to-discharge distribution by patients' age (*bottom*). The kernel density for the intervals from onset to admission, onset to death, and onset to discharge were plotted by using the Gaussian kernel (21).

sample is unknown. Future research should closely examine the relative merits and drawbacks of different statistical approaches to estimating this critical distribution, since such estimates are central to public health and infection control policymaking.

Our analysis of the onset to admission interval shows a progressive shortening of time from clinical onset of symptoms to presentation at the hospital, probably because of heightened community awareness of SARS and a high in-

Figure 6. **Nonparametric probabilities of survival and discharge.**



dex of suspicion among health care providers as the epidemic unfolded (22). Coupled with the observation that SARS almost exclusively manifests as a florid clinical syndrome requiring inpatient treatment and only very rarely as a subclinical or mild infection (that is, with no asymptomatic carriers of the disease [25, 30]), reducing the onset-to-admission interval to a minimum (that is, 2 days by the end of the Hong Kong epidemic) is possible and can be an effective public health control measure. Since almost no asymptomatic or even mildly symptomatic cases of SARS have occurred, infected individuals can recognize their own illness relatively easily and thus can promptly present themselves to the health care system. This allows the rapid isolation of infectious individuals, hence reducing the effective infectious period and the risk for transmission. Such was empirically observed in Singapore, where generation of secondary infections by index cases was substantial only if the onset-to-admission (isolation) interval exceeded 5 days (23). However, shortening the time between first symptoms and the initiation of treatment on hospitalization does not seem to increase the probability of survival. More generally, clinical studies of the typical course of infection in patients with SARS coronavirus suggests that the average peak infectiousness may occur some 8 to 9 days after onset of clinical symptoms (8). This biological pattern, which is very atypical for most respiratory tract or gastrointestinal tract infections, implies that prompt isolation after onset of clinical symptoms is a very effective public health measure for this particular infection. This observation also partly explains the high fraction of cases that occurred in health care workers in Hong Kong, Singapore, Taipei, and Toronto, since they had contact with patients during their peak infectiousness phase (14, 15, 31, 32).

The onset-to-death and onset-to-discharge-after-recovery distributions add substantial information to the natural history of the disease process (mostly among treated patients) and underline the importance of patients' age and sex in determining the course of illness. They allow future clinicians to understand the relative distributions of time to clinical outcomes and compare SARS in this outbreak to that of future outbreaks should they occur. The lower mean and variability in the onset-to-death interval distribution among the deceased elderly patients were probably due to their relative fragility and higher prevalence of comorbid conditions. On the other hand, while factors such as post-SARS disability and treatment complications might have led to a longer hospital stay for the elderly survivors, some of these patients were hospitalized for treatment of other diseases after recovery from SARS. The modal peak of the onset-to-discharge interval distribution at around 21 days in **Figure 5** (*bottom*) was, to an extent, an artifact of administrative guidelines of the minimum 21 days of hospitalization, which had been in effect since early April 2003.

Our previous estimation of epidemiolgic variables and case-fatality ratios during an ongoing epidemic is complicated by the open cohort problem of censoring, such that ascertaining who will eventually die or be discharged among those still hospitalized is impossible at the time of the analysis. This is further complicated by the temporal evolution of the epidemic, with incident cases continually being added to the pool of infected individuals (4). In this analysis of all 1755 consecutive cases in Hong Kong, we observed the outcomes in all cases. Hence, issues about censoring do not apply.

Although the overall case-fatality ratio was 17.2%, this average figure masks the substantial variation in case fatality by age. Male sex, more severe illness on presentation as proxied by lactate dehydrogenase level, and the presence of preexisting comorbid conditions were also significantly associated with a high case-fatality rate in the multivariable analysis. The timing of ribavirin administration did not seem to statistically significantly influence clinical outcome, possibly because of residual confounding or insufficient power to detect a difference given that most patients were treated. We caution that our observations from the model are tentative and must be externally confirmed in other settings given the many remaining uncertainties involving patient's clinical course; other treatments received; and the temporal evolution of triage, diagnosis, and care patterns throughout the epidemic. Previous analyses of case-fatality predictors have examined only small, hospital-based data sets with limited information on a comprehensive range of personal and clinical variables, although their findings were similar to ours, such as the effects of age, sex, comorbid conditions, and high lactate dehydrogenase levels on mortality (14, 15, 33). One weakness in analysis of all the major SARS outbreaks was insufficient attention given to the need to construct databases of treatment on the basis of information from all clinical settings that would permit analyses with sufficient patient numbers of what treatments worked best for what type of patient. In other jurisdictions, treatment data were not shared among clinical settings in order to create sufficient numbers of patients to permit analysis. In this context, even with the largest case cohort in Hong Kong, statistical power is insufficient to examine all the important factors that might influence case fatality. More detailed analysis involving other relevant clinical factors, such as the use of noninvasive assisted ventilation or other medications (for example, lopinavir–ritonavir combination) and associated timing, as well as longitudinal observations of clinical and laboratory variables, should be undertaken to clarify some of the unresolved issues.

Ideally, definitive answers to the best treatment regimen for patients with SARS require large randomized, controlled trials with clear outcomes defined a priori and sufficiently long follow-up. Such trials would need to monitor the possible side effects of candidate drugs, including the putative association of large doses of pulsed steroids with the subsequent development of avascular necrosis in some patients versus such complications being part of the clinical picture of SARS. In the heat of a crisis, however, randomized, controlled trials are typically not possible. As such, observational studies based on amalgamated data sets from different clinical settings are the only way to assess treatment value. In drawing conclusions from such analyses, bias may be present in patient choice for any given treatment, and this must be considered during interpretation.

More generally, public health authorities worldwide should establish well-designed and appropriately resourced protocols of randomized, controlled trials to properly evaluate the efficacy of various management strategies should a SARS outbreak recur (34). Although SARS is unlikely to return as a large epidemic across many different countries like the 2003 outbreak, clinical investigators must recognize the importance of collaboration on multinational, multicenter epidemiologic studies or clinical trials to increase the power to detect moderate effects of treatment regimens and associated risk factors (34, 35).

From University of Hong Kong, Government of the Hong Kong Special Administrative Region, and Hong Kong Hospital Authority, Hong Kong, China, amd Imperial College, University of London, London, United Kingdom.

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Requests for Single Reprints: Tai-Hing Lam, MD, FFPH, Department of Community Medicine, 21 Sassoon Road, Faculty of Medicine Building, University of Hong Kong, Pokfulam, Hong Kong, China; e-mail, commed@hkucc.hku.hk.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Zhong NS, Zheng BJ, Li YM, Poon, Xie ZH, Chan KH, et al.** Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. Lancet. 2003;362:1353-8. [PMID: 14585636]

2. **World Health Organization.** Consensus Document on the Epidemiology of Severe Acute Respiratory syndrome (SARS). Geneva: Department of Communicable Disease Surveillance and Response, World Health Organization; 2003.

3. **Guan Y, Zheng BJ, He YQ, Liu XL, Zhuang ZX, Cheung CL, et al.** Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. Science. 2003;302:276-8. [PMID: 12958366]

4. **Donnelly CA, Ghani AC, Leung GM, Hedley AJ, Fraser C, Riley S, et al.** Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. Lancet. 2003;361:1761-6. [PMID: 12781533]

5. **World Health Organization.** Use of Laboratory Methods for SARS Diagnosis. Geneva: World Health Organization; 2003. Accessed at www.who.int/csr/sars/labmethods/en/ on 23 February 2004.

6. **Fouchier RA, Osterhaus AD.** Laboratory tests for SARS: powerful or peripheral? CMAJ. 2004;170:63-4. [PMID: 14707221]

7. **Rainer TH, Cameron PA, Smit D, Ong KL, Hung AN, Nin DC, et al.** Evaluation of WHO criteria for identifying patients with severe acute respiratory syndrome out of hospital: prospective observational study. BMJ. 2003; 326:1354-8. [PMID: 12816820]

8. **Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, Poon LL, et al.** Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet. 2003;361:1767-72. [PMID: 12781535]

9. **Tang P, Louie M, Richardson SE, Smieja M, Simor AE, Jamieson F, et al.** Interpretation of diagnostic laboratory tests for severe acute respiratory syndrome: the Toronto experience. CMAJ. 2004;170:47-54. [PMID: 14707219]

10. **Poon LL, Chan KH, Wong OK, Yam WC, Yuen KY, Guan Y, et al.** Early diagnosis of SARS coronavirus infection by real time RT-PCR. J Clin Virol. 2003;28:233-8. [PMID: 14522060]

11. **Gomez G, Calle ML, Oller R.** Frequentist and Bayesian approaches for interval-censored data. Statistical Papers. 2004;45:139-73.

12. **Leung GM, Rainer TH, Lau FL, Wong IO, Tong A, Wong TW, et al.** A clinical prediction rule for diagnosing severe acute respiratory syndrome in the emergency department. Ann Intern Med. 2004;141:333-42.

13. **Lee N, Hui D, Wu A, Chan P, Cameron P, Joynt GM, et al.** A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med. 2003;348:1986-94. [PMID: 12682352]

14. **Booth CM, Matukas LM, Tomlinson GA, Rachlis AR, Rose DB, Dwosh HA, et al.** Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. JAMA. 2003;289:2801-9. [PMID: 12734147]

15. **Tai DY, Lew TW, Loo S, Earnest A, Chen MI.** Clinical features and predictors for mortality in a designated national SARS ICU in Singapore. Ann Acad Med Singapore. 2003;32:S34-6. [PMID: 14968728]

16. **King G, Honaker J, Joseph A, Scheve K.** Analyzing incomplete political science data: an alternative algorithm for multiple imputation. American Political Science Review. 2001;95:49-69.

17. **Honaker J, Joseph A, King G, Scheve K, Singh N.** AMELIA: A Program for Missing Data. Accessed at http://gking.harvard.edu/amelia/ on 28 May 2004.

18. **Rubin DB.** Multiple Imputation for Nonresponse in Surveys. New York: Wiley; 1987.

19. SARS Expert Committee. SARS in Hong Kong: From Experience to Action. Hong Kong: Government Printers; 2003.

20. **Lai PC, Wong CM, Hedley AJ, Lo SV, Leung PY, Kong J, Leung GM.** Understanding the spatial clustering of severe acute respiratory syndrome (SARS) in Hong Kong. Environ Health Perspect. 2004 [In press].

21. **Wand MP, Jones MC.** Kernel Smoothing. London: Chapman & Hall; 1995.

22. **Leung GM, Lam TH, Ho LM, Ho SY, Chan BH, Wong IO, et al.** The impact of community psychological responses on outbreak control for severe acute respiratory syndrome in Hong Kong. J Epidemiol Community Health. 2003;57:857-63. [PMID: 14600110]

23. **Lipsitch M, Cohen T, Cooper B, Robins JM, Ma S, James L, et al.** Transmission dynamics and control of severe acute respiratory syndrome. Science. 2003;300:1966-70. [PMID: 12766207]

24. **World Health Organization.** Summary of Probable SARS Cases with Onset of Illness from 1 November 2002 to 31 July 2003. Accessed at www.who.int/csr/sars/country/table2004_04_21/en/ On 26 May 2004.

25. **Leung GM, Chung PH, Tsang T, Lim W, Chan SKK, Chau P, et al.**

SARS-CoV antibody prevalence in all Hong Kong patient contacts. Emerg Infect Dis. 2004;10:1653-6.

26. **Hon KL, Leung CW, Cheng WT, Chan PK, Chu WC, Kwan YW, et al.** Clinical presentations and outcome of severe acute respiratory syndrome in children. Lancet. 2003;361:1701-3. [PMID: 12767737]

27. **Ng PC, Lam CW, Li AM, Wong CK, Cheng FW, Leung TF, et al.** Inflammatory cytokine profile in children with severe acute respiratory syndrome. Pediatrics. 2004;113:e7-14. [PMID: 14702488]

28. **Riley S, Fraser C, Donnelly CA, Ghani AC, Abu-Raddad LJ, Hedley AJ, et al.** Transmission dynamics of the etiological agent of SARS in Hong Kong: impact of public health interventions. Science. 2003;300:1961-6. [PMID: 12766206]

29. **Centers for Disease Control and Prevention.** Public Health Guidance for Community-Level Preparedness and Response to Severe Acute Respiratory Syndrome (SARS). Version 2. Supplement D: Community Containment Measures, Including Non-Hospital Isolation and Quarantine. Atlanta: Centers for Disease Control and Prevention; 8 January 2004. Accessed at www.cdc.gov/ncidod/sars/guidance/D/index.htm on 14 February 2004.

30. **Rainer TH, Chan PK, Ip M, Lee N, Hui DS, Smit D, et al.** The spectrum of severe acute respiratory syndrome-associated coronavirus infection. Ann Intern Med. 2004;140:614-9. [PMID: 15096332]

31. **Fraser C, Riley S, Anderson RM, Ferguson NM.** Factors that make an infectious disease outbreak controllable. Proc Natl Acad Sci U S A. 2004;101: 6146-51. [PMID: 15071187]

32. **Hsieh YH, Chen CW, Hsu SB.** SARS outbreak, Taiwan, 2003. Emerg Infect Dis. 2004;10:201-6. [PMID: 15030683]

33. **Wong WW, Chen TL, Yang SP, Wang FD, Cheng NC, Kuo BI, et al.** Clinical characteristics of fatal patients with severe acute respiratory syndrome in a medical center in Taipei. J Chin Med Assoc. 2003;66:323-7. [PMID: 12889500]

34. **Naylor CD, Chantler C, Griffiths S.** Learning from SARS in Hong Kong and Toronto. JAMA. 2004;291:2483-7. [PMID: 15161900]

35. **Lam TH, Leung GM.** Geoethnic-sensitive and cross-culture collaborative epidemiological studies [Editorial]. Int J Epidemiol. 2003;32:178-80. [PMID: 12714529]

36. **Stuart A, Ord JK.** Kendall's Advanced Theory of Statistics. London: Edward Arnold; 1994.

APPENDIX

Case Definitions of SARS

At the beginning of the SARS outbreak in Hong Kong, SARS was defined by the presence of new radiologic infiltrates compatible with pneumonia; body temperature of 38 °C or greater or history of such in the last 2 days; and presence of at least 2 of the following: chills at any time in the last 2 days, new or increased cough, new or increased shortness of breath, or typical physical findings of consolidation.

Exclusion criteria were clinically significant bronchiectasis, leukocytosis on admission, chest radiograph showing lobar consolidation, or already known pathogen. On 10 April 2003, the case definition of SARS was updated with the changes in the WHO case definition and with local clinical experience. The revised case definition of SARS was the presence of new radiologic infiltrates compatible with pneumonia; body temperature of 38 °C or greater or history of such in the last 2 days; and the presence of at least 2 of the following: history of chills in the past 2 days, cough (new or increased cough) or breathing difficulty, general malaise or myalgia, or known history of exposure.

Exclusion criteria were replaced by only 1 variable: A case would be excluded if an alternative diagnosis could fully explain the illness. By using this updated case definition, the Hong Kong Hospital Authority eSARS registry included 1755 patients.

Symptom Onset Date

Symptom onset date is defined as the date on which the patient first experienced symptoms of SARS. We determined the symptom onset date on the basis of 2 sources. Upon a patient's entry into the eSARS registry, the Hong Kong Department of Health administered 2 questionnaires (a case questionnaire and a case contact survey), mostly through telephone interviews, to all patients in the eSARS registry. Frontline nurses later captured patients' symptom onset date from physicians' admission notes and entered them into the Hong Kong Hospital Authority eSARS database. There were minor differences between the 2 sources of data, and we adopted the former set of data in this analysis to minimize recall and transcription bias.

Admission Date

Admission date is the patient's date of admission for the SARS episode. For SARS episodes that started during a patient's hospitalization for a non-SARS illness, admission date refers to the date of admission for the initial non-SARS illness.

Biphasic Linear Model

A biphasic linear model was fitted to the onset to admission interval, with onset category as the independent variable to test for temporal changes in this key variable throughout the duration of the 2003 epidemic in Hong Kong (36). This biphasic linear model may be important because it measures how quickly infectious individuals in the community were isolated and treated in hospitals. In the biphasic linear model, we constrained the 2 linear regression segments to meet at the same breakpoint corresponding to a particular onset category. For each breakpoint (11 breakpoints in total), we solved the model by the maximum likelihood approach (36), and the final breakpoint was associated with the model with the largest likelihood.

Current Author Addresses: Drs. G.M. Leung, Hedley, Ho, Thach, and Lam, Ms. Chau, and Ms. I.O.L. Wong: Department of Community Medicine and School of Public Health, University of Hong Kong, 21 Sassoon Road, Pokfulam, Hong Kong, China.
Drs. Ghani, Fraser, Anderson, Donnelly, Riley, and Ferguson: Department of Infectious Disease Epidemiology, Imperial College London, St Mary's Campus, Norfolk Place, London W2 1PG, United Kingdom.
Drs. Tsang and P.-Y. Leung: Department of Health, Government of the Hong Kong Special Administrative Region, Wu Chung House, Wanchai, Hong Kong, China.
Drs. V. Wong and Chan and Ms. Tsui: Hong Kong Hospital Authority, 147 Argyle Street, Kowloon, Hong Kong, China.
Dr. Lo: Health, Welfare and Food Bureau, Government of the Hong Kong Special Administrative Region, Murray Building, Central, Hong Kong, China.

Author Contributions: Conception and design: G.M. Leung, A.J. Hedley, T.-H. Lam.
Analysis and interpretation of the data: G.M. Leung, A.J. Hedley, L.-M. Ho, T.Q. Thach, A.C. Ghani, C.A. Donnelly, C. Fraser, S. Riley, N.M. Ferguson, R.M. Anderson, T.-H. Lam.
Drafting of the article: G.M. Leung.
Critical revision of the article for important intellectual content: A.C. Ghani, C.A. Donnelly, C. Fraser, S. Riley, N.M. Ferguson, R.M. Anderson, V. Wong, J.C.K. Chan, E. Tsui, S.-V. Lo.
Final approval of the article: G.M. Leung, A.J. Hedley, L.-M. Ho, I.O.L. Wong, A.C. Ghani, C.A. Donnelly, C. Fraser, S. Riley, N.M. Ferguson, R.M. Anderson, S.-V. Lo, T.-H. Lam.
Provision of study materials or patients: T. Tsang, P.-Y. Leung, V. Wong, J.C.K. Chan, E. Tsui.
Statistical expertise: L.-M. Ho, P. Chau, I.O.L. Wong, T.Q. Thach.
Obtaining of funding: G.M. Leung, A.J. Hedley, T.-H. Lam.
Administrative, technical, or logistic support: P. Chau, T. Tsang, P.-Y. Leung, V. Wong, J.C.K. Chan, S.-V. Lo.
Collection and assembly of data: P. Chau, I.O.L. Wong, T.Q. Thach, T. Tsang, P.-Y. Leung, E. Tsui.

Appendix Table 1. **Characteristics of Patients with Severe Acute Respiratory Syndrome, Case-Fatality Ratios, and Associated Adjusted Odds Ratios***

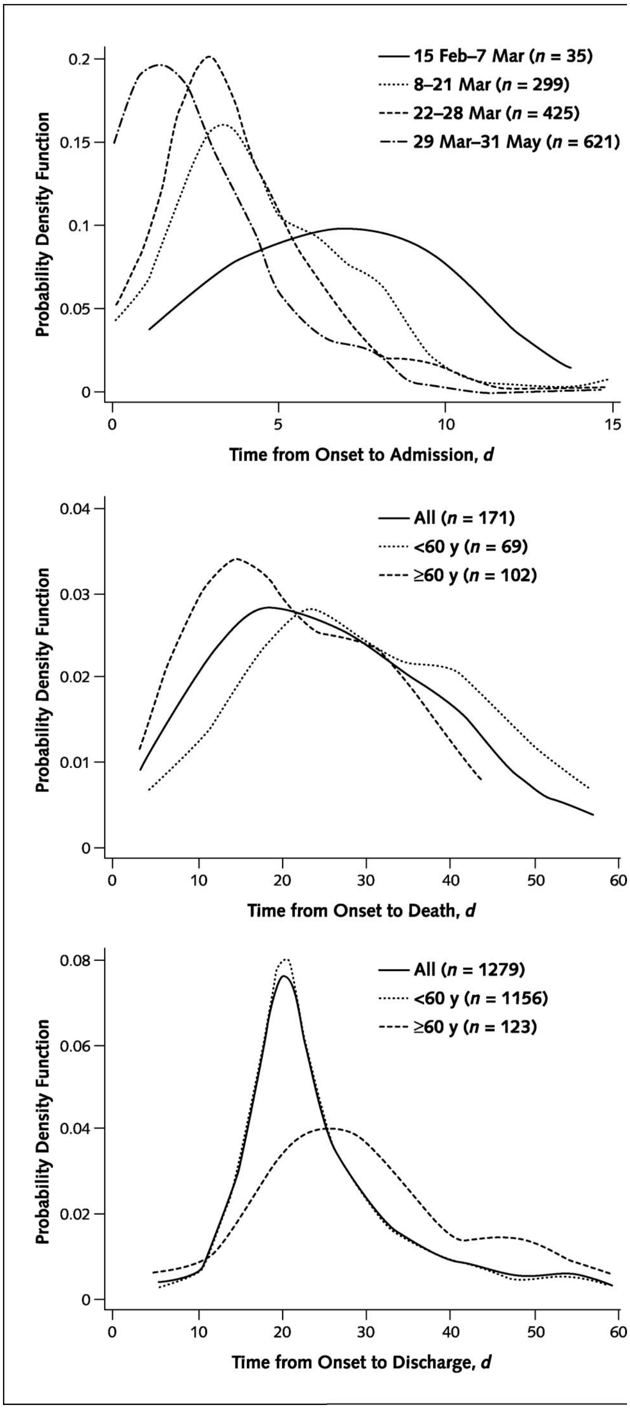
Characteristic	Patients, *n* (%) (*n* = 1467)	Case-Fatality Ratio, %	Adjusted Odds Ratio (95% CI)	*P* Value†
Sex				
Women	861 (58.7)	9.2	1	—
Men	606 (41.3)	15.2	1.5 (1.0–2.2)	
Age				
≤39 y	762 (51.9)	2.2	1	<0.001
40–59 y	476 (32.5)	10.9	4.7 (2.6–8.4)	
≥60 y	229 (15.6)	44.5	20.6 (10.8–39.6)	
Health care worker				
No	1072 (73.1)	15.2	1	—
Yes	395 (26.9)	2.0	0.6 (0.2–1.3)	
Atypical symptoms				
No	1236 (84.3)	11.0	1	—
Yes	16 (1.1)	43.8	1.5 (0.5–4.4)	
Unknown because of missing data	215 (14.7)	13.0	—	
Infection cluster				
Not hospital- or community-acquired	128 (8.7)	11.7	1	—
Amoy Gardens residential buildings	312 (21.3)	8.7	1.0 (0.5–2.2)	
Amoy Gardens nearby‡	109 (7.4)	11.9	1.1 (0.4–2.8)	
Non–Amoy Gardens residential buildings	42 (2.9)	21.4	2.4 (0.8–7.0)	
Hospitals or elderly or nursing homes	744 (50.7)	12.4	0.6 (0.3–1.2)	
Air flight	19 (1.3)	15.8	2.4 (0.5–11.4)	
Imported	50 (3.4)	12.0	0.7 (0.2–2.1)	
Unknown sources	63 (4.3)	9.5	0.7 (0.2–2.1)	
Symptom onset date				
15 February–14 March	184 (12.5)	12.0	1	0.04
15–28 March	587 (40.0)	10.2	0.6 (0.3–1.3)	
29 March–11 April	405 (27.6)	9.6	0.4 (0.2–0.8)	
12–25 April	168 (11.4)	10.1	0.2 (0.1–0.6)	
26 April–31 May	123 (8.4)	26.8	0.6 (0.2–1.3)	
Onset-to-admission interval				
1 d	183 (12.5)	6.6	1	0.11§
2–3 d	486 (33.1)	10.1	1.2 (0.6–2.7)	
4–5 d	300 (20.4)	6.3	0.6 (0.2–1.5)	
6–7 d	154 (10.5)	9.1	0.7 (0.3–2.0)	
≥8 d	111 (7.6)	9.9	0.7 (0.2–2.0)	
Admitted on or before symptom onset date	233 (15.9)	28.3	2.2 (1.0–4.9)	
Preexisting comorbid conditions				
No	1221 (83.2)	7.2	1	—
Yes	246 (16.8)	33.7	1.9 (1.2–3.0)	
Lactate dehydrogenase level on admission‖				
≤0.79	313 (21.3)	6.6	1	0.01
0.79–0.99	317 (21.6)	7.6	1.0 (0.5–1.9)	
0.99–1.37	312 (21.3)	11.5	1.4 (0.7–2.5)	
>1.37	313 (21.3)	18.8	2.1 (1.1–4.0)	
Not measured	212 (14.5)	15.2	—	
Initiation of ribavirin therapy from symptom onset				
Treatment not prescribed	51 (3.5)	29.4	1	>0.2
Prescribed on day of symptom onset	25 (1.7)	4.0	0.3 (0.0–2.8)	
1–3 d	480 (32.7)	11.1	1.4 (0.6–3.6)	
4–6 d	499 (34.0)	10.0	1.1 (0.4–2.7)	
≥7 d	412 (28.1)	12.5	1.0 (0.4–2.5)	

* All variables were entered and adjusted for each other in the logistic model. Multiple imputation methods were used to handle missing data items, and results are based on the analysis of all patients.
† For linear trend.
‡ "Amoy Gardens nearby" refers to cases of severe acute respiratory syndrome that occurred in the immediate neighborhood of Amoy Gardens and were believed to be linked to the superspreading event, but the patients were not residents of the housing estate.
§ Applies to only the first 5 subcategories.
‖ Reported as a ratio to upper limit of normal.

Appendix Table 2. **Maximum Likelihood Estimates of Key Epidemiologic Variables**

Variable	Patients, n	Mean Length of Time (95% CI), *d*	Median Length of Time, *d*	10th Percentile, *d*	90th Percentile, *d*
Time from infection to onset (incubation period)	68	4.7 (3.8–5.8)	—	—	—
Time from onset to admission					
15 February–7 March	35	6.7 (5.6–7.9)	7.0	2.0	11.0
8–14 March	144	4.7 (4.2–5.1)	4.0	2.0	8.0
15–21 March	155	4.4 (3.9–4.9)	4.0	1.0	8.0
22–28 March	425	3.7 (3.5–3.9)	3.0	1.0	7.0
29 March–4 April	217	2.7 (2.3–3.0)	2.0	0	6.0
5–11 April	171	2.5 (2.1–2.8)	2.0	0	5.0
12–18 April	90	2.8 (2.3–3.3)	2.0	0	6.0
19–25 April	54	2.4 (1.8–3.0)	2.0	0	4.0
26 April–2 May	36	2.7 (2.0–3.4)	2.5	0	5.0
3–9 May	23	2.7 (1.7–3.6)	3.0	0	5.0
10–31 May	30	2.1 (1.3–2.9)	2.0	0	5.0
Time from onset to death					
Men					
≤29 y	1	—	—	—	—
30–39 y	6	32.2 (16.4–48.0)	28.5	16.0	60.0
40–49 y	20	34.6 (26.3–42.8)	28.5	18.5	52.5
50–59 y	12	35.9 (28.6–43.3)	39.0	21.0	48.0
60–69 y	17	23.6 (18.0–29.1)	25.0	9.0	37.0
≥70 y	36	24.7 (19.9–29.4)	20.5	9.0	44.0
Women					
≤29 y	—	—	—	—	—
30–39 y	10	31.1 (21.2–41.0)	29.0	15.0	49.0
40–49 y	9	30.9 (18.5–43.3)	32.0	10.0	56.0
50–59 y	11	42.5 (29.1–56.0)	36.0	18.0	64.0
60–69	9	35.1 (19.4–50.8)	36.0	10.0	73.0
≥70 y	40	20.2 (15.4–25.0)	14.5	6.0	40.0
Time from onset to discharge from short-term care					
Men					
≤29 y	172	24.1 (22.9–25.3)	22.5	16.0	34.0
30–39 y	119	27.7 (25.3–30.2)	23.0	18.0	42.0
40–49 y	100	27.5 (24.7–30.2)	24.0	16.0	41.5
50–59 y	53	32.9 (27.6–38.2)	26.0	16.0	60.0
60–69 y	34	36.4 (28.6–44.2)	27.5	19.0	71.0
≥70 y	27	29.0 (22.7–35.3)	24.0	14.0	55.0
Women					
≤29 y	252	23.7 (22.6–24.8)	21.0	15.0	34.0
30–39 y	196	26.3 (24.5–28.1)	23.0	15.0	37.0
40–49 y	180	28.3 (26.2–30.3)	24.0	17.0	43.0
50–59 y	84	27.7 (24.8–30.6)	25.0	16.0	42.0
60–69 y	23	33.9 (27.7–40.1)	30.0	17.0	53.0
≥70 y	39	34.5 (27.1–42.0)	28.0	14.0	63.0

Appendix Figure 1. **Estimates of onset-to-admission, onset-to-death, and onset-to-discharge distributions.**



Estimates of time-dependent onset-to-admission distribution as a function of time of onset of clinical symptoms (*top*), onset-to-death distribution by patients' age (*middle*), and onset-to-discharge distribution by patients' age (*bottom*). The kernel density for the intervals from onset to admission, onset to death, and onset to discharge were plotted by using the Gaussian kernel (21).

Appendix Figure 2. **Nonparametric probabilities of survival and discharge.**